Manuscript ID BMJ.2018.045335 entitled "Cause-specific mortality risk and burden associated with non-optimum ambient temperature in 272 main Chinese cities"

Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: Sophie Cook (chair), Rafael Perera (statistician), Wim Weber, Jose Merino, Elizabeth Loder, John Fletcher, Georg Roggla, Daoxin Yin, Tiago Villanueva

Decision: Put points

Detailed comments from the meeting:

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

Please also respond to these additional comments by the committee:

Response: We appreciate these helpful comments on our manuscript. According to these comments, we re-ran all the models and revised our manuscript accordingly.

- Our statistician made the following comments:

A pretty complex modelling study. This is necessary given the data and the question asked. Several of the methods used here are relatively new but seem appropriate. Nevertheless, I would like them to answer a few questions regarding these models:

1) How robust is the estimation of time lags. Is this based on an automatic selection process? How can we determine consistency of this across regions/cities?

Response: This is a good question on model selection. We empirically determined the time lag (up to 21 days) according to previous multicity studies in this area (see lines 154-157). In multicity time-series studies, it is most common to empirically adopt a set of uniform model parameters to make comparable in terms of model structure within the same study, and then conduct sensitivity analyses on model parameters if necessary.

In this revision, we conducted a sensitivity analysis using alternative maximum lag. We found the minimum-mortality percentile of temperature distribution, minimum-mortality temperature, relative risks and attributable fractions increased from a maximum lag of 7 days to 21 days, and remained almost unchanged when the maximum lag was extended to 28 days. Therefore, the use of a maximum lag of 21 days was appropriate in this study. Please refer to lines 215-217 in the statistical analysis section and lines 345-347 in the results section.

2) The estimation of a city specific MMT and the recentering based on these,

does this approach minimise potential bias or create any?

Response: In the first-stage single-city analysis, we did not center the exposure-response curves because we only needed the coefficients and variance-covariance matrix to combine these multiple curves, but herein the risk estimates were inaccurate. Therefore, re-centering the curves according to the city-specific MMTs could minimize the potential bias and obtain accurate risk estimates in the second-stage meta-analysis. Please refer to lines 167-169.

3) The lack of pollutant data is likely to be a major confounder, particularly as there are relevant interactions between pollutants and different temperatures. Unless all sites have same contamination levels, this is likely to be affecting the results.

Response: This is a great suggestion to make our results more reliable. In this revision, we controlled for fine particulate matter and ozone (as two most representative indicators of air pollution) in an additional sensitivity analysis. We did not find apparent changes on the estimates on relative risks and attributable fractions associated with non-optimum temperatures, which were generally consistent with previous temperature studies. Please refer to lines 217-218 in the statistical analysis and lines 348-350 in the result section.

We did not include this adjustment in main analyses because there were a considerable proportion of missing data on air pollution in the 3-year study period (see lines 245-247).

Issues 2 and 3 stem from some lack of clarity in their Stage 2 modelling. Reviewers have relevant comments on the need for clarity in their meta-regression (meta-analysis) approach. Some of the city characteristics would need to be included here.

Response: In the original version, we had neglected some technical details in the second-stage meta-analysis to avoid a lengthy description of statistical modelling in this journal. For example, city-level characteristics had already been included in the meta-regression analysis, but were not mentioned in the original version of the manuscript. Following the comments of editors and reviewers, in this revision we added more city characteristics in the second-stage modelling and provided more technical details accordingly. Please refer to lines 160-163 and lines 167-176.

Generally it seems well carried out.

The comments of editors

- Several editors were in favour since, even though the findings are in line with other studies, it is a large, descriptive study that covers most of China and is in line with BMJ’s interest in climate change.

Response: We appreciate these positive comments on our manuscript. This study provided ample and somewhat novel evidence on cause-specific mortality risk and burden associated with non-optimum ambient temperature as well as the individual- and city- level effect modifiers. All these findings are helpful to future disease burden assessment and to design optimum clinical and public health practice that are expected to reduce disease burden caused by current and future abnormal weather. Please refer to lines 475-485.

- One editor suggested that you discuss the potential impact of central heating in Northern China (areas in the north of the Yangtze River) during winter, even though data might be limited. And it might be more reader-friendly if you can mention in the abstract the temperature range in Degree/Fahrenheit for “moderate cold", "moderate heat", etc.

Response: This is a great suggestion to improve our manuscript. In this revision, we explored the modification by duration of central heating in the mortality risk and burden due to non-optimum temperatures in Northern China (see lines 209-211 in the statistical analysis). We found that the mortality risk and burden associated with cold temperature were more prominent in cities characterized by longer duration of central heating (see lines 334-338 in the result section).

Additionally, we added the definitions of moderate cold, moderate heat, extreme cold and extreme heat temperatures. Please refer to lines 21-22.

- Another editor said that even though the data is national in scope, there are relatively few cities from some regions (e.g. alpine region). She wondered if you discuss more the fact why cold seems to be worse than heat overall, and that moderate cold and moderate heat are more important than extremes of either because they account for more overall exposure.

Response: We understand this concern. The number of cities differed by climatic zones according to the climatic divisions (see lines 100-113) and the inclusion criteria (see lines 86-88), which may attenuate the comparability of our findings in different climatic zones. In this revision, we listed this as a limitation (see lines 461-463).

Following this comment, we added more interpretations on the two respects of comparisons in the discussion section (see lines 386-393).

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

Response: We prepared point-to-point replies to these comments and have revised the manuscript accordingly.

Comments from Reviewers

Reviewer: 1

Recommendation:

Comments:

This is an interesting study to examine the impacts of ambient temperatures on cause-specific mortality in China, with a large data set. This study provides additional evidence on the impacts of temperature on mortality in China. Particularly, the authors use a relatively complex analytical framework, involving sophisticated designs and statistical techniques. The results are neatly summarized and interpreted, and then carefully discussed. My comments mainly refer to analytical strategies, which do not require major changes to the structure of the manuscript.

Response: We appreciate the positive comments on our manuscript.

1) The Design of abstract, the current version only reflects the first stage but no information for second stage. Suggest to add statement for second stage analysis, like "Time series analysis with DLNM was used to estimate city-specific associations in the first stage, then meta-analysis strategy was applied to model the effect estimates in the second stage ".

Response: Done as suggested (see lines 4-7).

2) The conclusion of abstract should be more specific. The current version is broad.

Response: We revised the conclusion accordingly (lines 32-38).

3) The second stage analysis is expressed a little unclearly. It is not clear which independent variables are used as predictors in the BLUP. Usually, BLUP (a special prediction function of meta-regression) is used to predict city-specific association, with city level characteristics (e.g., mean temperature, temperature range, GDP, latitude, or others).

Response: We apologize for neglecting such information in presenting our statistical analysis section. In the original analysis, we had already included city-specific annual-mean temperature, temperature range and indicators for climatic zones as meta predictors in BLUP estimations (i.e., the multivariate meta-regression analysis). The construction of the BLUP was just the same as the paper published in the Lancet (Gasparrini, 2015).

Following this suggestion, we further added GDP per capita and urbanization rates in BLUP estimations, which were also significant effect modifiers according to our preliminary heterogeneity analysis. We did not include latitude because it is highly correlated with annual-mean temperature. Please refer to lines 160-163.

4) Usually, national level association is pooled by meta-analysis or meta-regression with intercept only (no predictors, meta-analysis is a special case of meta-regression). It is ok that the authors use BLUP to predict national

level association, but they should develop a meta-regression with city level characteristics as predictor (comment #3), then calculate the average of city level characteristics as predictor to predict national level association. Or if the authors used other method, it should be clarified. It is the same to pool regional associations.

Response: Thanks for raising this important issue that we have neglected to describe in the statistical analysis section. As explained in the above response, such multivariate meta-regression analysis had already been done following the investigation published in the Lancet (Gasparrini, 2015). Following this suggestion, we further added GDP per capita and urbanization rates in BLUP estimations. Please refer to lines 160-163.

5) "We assessed the potential effect modification by city-level characteristics on climate, geography and socioeconomic conditions." This part is a meta-regression. Actually, it can be used to predict city level association (with city characteristics), regional level association (with region as predictor), and national level association (intercept only). I suggest to use this method as the main second stage analysis. This will make the analysis clear and easy to understand by readers. However, it is optional if the authors could clarified their method clearly.

Response: We sincerely appreciate these instructive suggestions on our manuscript. As explained in the aforementioned replies, virtually we had already done such multivariate meta-regression analysis, but had neglected to mention it in the statistical analysis section. In this revision, we provided more details to clarify this issue. Please refer to lines 160-163.

6) The scale of x-axis of Figure should be percentile at national (or regional) level association, because the authors put the spline knots at the same percentile of temperature for each city, not the absolute temperature. So the pooled association represents relative scale (percentile scale).

Response: We understand this concern and apologize for neglecting this information in presenting the second-stage statistical analysis. In this revision, we provided technical details about the plotting of exposure-response relationship curves and lag structures. Please refer to lines 169-175.

The exposure-response relationship curves were actually estimated by the aforementioned models but were re-centered at the city-specific minimum-mortality temperatures (not the minimum-mortality percentiles). Herein we specified the curves with two boundary knots that corresponded to the averages of minimum and maximum temperature in each city during the study period. This choice generates pooled exposure-response curves with the uniform distribution of absolute temperatures at national or regional levels, which were more reader-friendly than the use of spline knots at percentiles of temperature for each city (that leads to relative percentiles as exposures in this curve). In addition, we illustrated the lag patterns in mortality risks associated with the extreme cold temperature (2.5th percentile) and the extreme hot temperatures (97.5th percentile).

7) Suggest to add range of MMP and MMT into Table 1.

Response: Following this suggestion, we provided descriptive statistics (including the mean, ranges and percentiles) of MMP and MMT for each cause of mortality in table SM1 in the web appendix. Please refer to lines 273-275.

8) It might be good to discuss the results for age group, sex, and education level.

Response: Done as suggested. Please refer to lines 418-421.

Additional Questions:

Please enter your name: Yuming Guo

Job Title: Associate Professor

Institution: Monash University

Reimbursement for attending a symposium?: No

A fee for speaking?: No

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Reviewer: 2

Recommendation:

Comments:

Chen et al. quantified the disease burden due to non-optimum temperature in in 272 main Chinese cities, across different climatic zones, demographic and socioeconomic factors. This comprehensive picture can inform public health policy and protection of vulnerable populations in China. Improved discussion and highlights are needed on the novelty of methodology and findings and differentiation from the earlier papers of Gasparrini et al who have reported that:

1) Both cold and heat are associated with increased risks of mortality;

2) Moderate cold is responsible for the majority of the temperature-related disease burden; and

3) Areas with warmer climate usually are subject to larger effects of cold, whereas cold areas are more susceptible to hot effects.

Response: We appreciate the generous comments on our manuscript. In the introduction section of the original version, we had already stated the possible shortcomings of previous studies that would be addressed in our study (see line 66-72), and summarized the novelty of our findings in the section of “What this study adds” in the Summary box (lines 486-502).

We added comparisons between the Gasparrini’s (Lancet, 2015) results and our findings on minimum-mortality percentiles (see lines 377-380) and attributable fractions (see lines 383-385). We further discussed our novel contributions (see lines 394-439) and novelty/strengths (see lines 441-450).

For example, one novel contribution of the current manuscript can be the comparison and discussion of cause-specific and system-specific (cardiovascular vs. respiratory) disease burdens. The systemic evaluation of latitude and longitude effects in China can also be highlighted.

Response: We appreciate these suggestions. In our original version, we reinforced the comparison of the cause-specific disease burden with previous findings and the biological interpretations of these differentiated disease burden (see lines 394-413)

On the other hand, we revised and reinforced the results of effect modification in terms of demographic, climatic, and socioeconomic characteristics (see lines 414-439).

Minor comments:

1. BULP → BLUP

Response: Revised.

2. Line 434-436: '… attributable fraction of … on …' should be a typo.

Response: We revised this sentence as "we estimated the attributable fractions of total and cause-specific mortality associated with non-optimum temperatures and their compositions (moderate cold, moderate heat, extreme cold and extreme heat" (see line 497-498)

3. Figure 5 can be improved by presenting the 3 factors separately …

Response: Following this suggestion, we improved this figure by adding three labels (age, gender and education).

References:

1. Gasparrini A, Guo Y, Hashizume M, Lavigne E, Zanobetti A, Schwartz J, Tobias A, Tong S, Rocklöv J, Forsberg B, Leone M, De Sario M, Bell ML, Guo YLL, Wu CF, Kan H, Yi SM, de Sousa Zanotti Stagliorio Coelho M, Saldiva PH, Honda Y, Kim H, Armstrong B. Mortality risk attributable to high and low

ambient temperature: a multicountry observational study. The Lancet. 2015;386(9991):369-375.

2. Vicedo-Cabrera AM, Sera F, Guo Y, Chung Y, Arbuthnott K, Tong S, Tobias A, Lavigne E, de Sousa Zanotti Stagliorio Coelho M, Hilario Nascimento Saldiva P, Goodman PG, Zeka A, Hashizume M, Honda Y, Kim H, Ragettli MS, Röösli M, Zanobetti A, Schwartz J, Armstrong B, Gasparrini A. A multi-country analysis on potential adaptive mechanisms to cold and heat in a changing climate. Environment International. 2018;111:239-246.

3. Gasparrini A, Guo Y, Hashizume M, Kinney P, Petkova EP, Lavigne E, Zanobetti A, Schwartz J, Tobias A, Leone M, Tong S, Honda Y, Kim H, Armstrong BG. Temporal variation in heat-mortality associations: a multicountry study. Environmental Health Perspectives. 2015;123(11):1200-1207.

4. Guo Y, Gasparrini A, Armstrong BG, Tawatsupa B, Tobias A, Lavigne E, Coelho MS, Pan X, Kim H, Hashizume M, Honda Y, Guo YL, Wu CF, Zanobetti A, Schwartz JD, Bell ML, Scortichini M, Michelozzi P, Punnasiri K, Li S, Tian L, Osorio Garcia SD, Seposo X, Overcenco A, Zeka A, Goodman P, Dang TN, Dung DV, Mayvaneh F, Saldiva PHN, Williams G, Tong S. Heat wave and mortality: a multicountry, multicommunity sudy. Environmental Health Perspectives 2017;125(8):087006.

Response: We acknowledged these useful references and cited some of them in this revised manuscript.

Additional Questions:

Please enter your name: Linwei Tian

Job Title: Associate Professor

Institution: The University of Hong Kong

Reimbursement for attending a symposium?: No

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Reviewer: 3

Recommendation:

Comments:

This paper is to quantify the cause-specific mortality risk and burden associated with non-optimum ambient temperature. They reported that 12.55% of total mortality was attributable to non-optimum temperatures and that fractions differed by death causes with 16.26% for cardiovascular diseases, 17.97% for coronary heart disease, 14.62% for stroke, 14.71% for ischemic stroke, 19.64% for hemorrhagic stroke, 10.16% for respiratory disease and 11.6% for chronic 23 obstructive pulmonary diseases. The authors applied widely used dlnm(distributed lag non-linear models) and the results are also comparable to the previous studies. Even though the study period is relatively short (2013-2015, 3 years), the authors performed large scale 272, city-wise analyses. And applied meta-regression analysis to have integrated information from the city-wise results. This manuscript provides valuable information on this research area. I have a few comments mainly on the analytic side.

Response: We appreciate the generous comments on our manuscript.

Exposure-response curve for small cities would be very instable, I expect. Do you think city is the best option for the first dlnm fitting? Bigger area than individual city, like province, would be better. What is your response?

Response: We appreciate the suggestion to increase the statistical power. However, the population size is not a big concern in single-city time-series analysis because the results from time-series models are expressed as relative risks (rather than the absolute coefficients). Furthermore, many provinces in China include more than 10 cities and cover a large area with diverse climatic, geographic and socioeconomical characteristics. Therefore, we can not perform the first-stage analyses at provincial levels.

RR(or excessive deaths) and AF have pros and cons. The authors extensively reported AF which indicates that AF would be better as an index. Please comment on this.

Response: We understand this issue. As one of the most common indicators in epidemiological studies, RR represents the magnitude of risk (probability of a death occurring) at a given temperature compared with the referent temperature in this study setting. However, AF is a more important indicator representing the relative contribution of non-optimum temperatures to the whole disease burden and is therefore one of the most understandable indicators of communicating health risks to the public. Therefore, we used comparable lengths of text and tables/figures to report RRs (including E-R curves and lag patterns) and AFs throughout the manuscript.

There are several papers indicating strong confounding of the season on the cold effect. Some even suggested that cold effect is not real, it is actually winter effect. I think most of the recent papers should be more cautious on cold effect. What do you think?

Response: This is a good comment on the broad area of temperature-related epidemiological studies. Consistent with most previous studies, we found larger and more prolonged effects and disease burden of low temperatures than effects of high temperatures (see lines 370-373 and lines 386-390). The cold effects need to be cautiously interpreted because of the possible residual confounding by the cold season and the influenza. We listed this as a limitation of this investigation (see lines 467-470)

In this revision, we increased the degree of seasonality control from 8 df to 12 df per year (see lines 143-145). The updated lag structure (Figure 3) of cold effects showed the lag period was shortened and the upward trends at lags longer than 15 days almost disappeared (see lines 257-259). Therefore, we updated our all analyses using 12 df per year in smoothness of seasonality.

Please discuss the effect of influenza on estimating the cold effect should also be discussed.

Response: We agree with this point. The effects of non-optimum temperature (especially cold temperature) need to be cautiously interpreted because of the possible residual confounding by the influenza. However, previous studies have revealed that the influenza accounted for a very small proportion of winter mortality and controlling for it would not substantially change the effect estimates of cold temperature. Please refer to lines 467-473 in the limitation section.

Additional Questions:

Please enter your name: Ho Kim

Job Title: Professor

Institution: Seoul National University

Reimbursement for attending a symposium?: No

A fee for speaking?: No

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Funds for research?: No

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Reviewer: 4

Recommendation:

Comments:

Based on daily numbers of deaths from non-accidental causes in 272 Chinese cities, the paper quantified the cause-specific mortality risk and burden associated with non-optimum ambient temperature. The authors performed comprehensive analyses and the statistical methods used were sound. This paper is interesting and generally written well. It added significant evidence to the literature on the contribution of ambient temperatures to cause-specific mortality. If the authors can answer all the questions given below then the paper should be reconsidered for publication.

Response: We appreciate the generous comments and have fully addressed the concerns raised by the reviewer.

1.Please provide more details to clarify the representativeness of the Disease Surveillance Point System of China. How many districts in each city involved in the system? The proportion of deaths registered in this system in each city, etc.

Response: In this revision, we provided more details about the representativeness of the Disease Surveillance Point (DSP) System of China. The surveillance points were randomly selected using an iterative method involving multistage stratification. The DSP system included 605 districts and counties (equal to districts at the administrative level in China) from almost all cities at or above the prefecture level. In each city, DSP covered one to eight districts/counties depending on the total population size of this city. The data from this death registry have been widely used in policy formulation and disease burden assessment in China and worldwide. In the present analysis, we included all cities covered by the system but excluded those with less than 3 non-accidental cities per day on average and those with no air quality monitoring data. Finally, we incorporated 272 cities in the present study. Please refer to lines 86-97.

The proportion of deaths registered by this system in the total deaths for each city was not available, which was also probably inaccurate because the death registry data outside the DSP system was not under strict quality control as done within the system in China. Alternatively, we provided the population size covered by the DSP system as well as the total population size (and the proportions) in all cities and each climatic zone. Please refer to lines 97-99 and lines 110-113 in the method section.

2. This study aimed to quantify mortality burden associated with non-optimum ambient temperature, while the authors only considered non-accidental deaths, probably leading to an underestimation of the burden. Is the reason for excluding accidental deaths that significant effects were not found? Several studies in US, Korea and China have reported the association between suicide mortality (one of main causes of accidental deaths) and ambient temperaturse. It would be of great interest to further investigate in this large-scale study. I

suggest reporting relevant results anyway.

Response: Good suggestion! We agree that suicide may be triggered by non-optimum ambient temperature according to some recent studies. However, our attempt to analyze its association was limited by the very few cases of suicide deaths recorded by the DSP system (less than 1 per day on average in most cities), which could not be adequately evaluated by the current analytic approach. In this revision, we added this as a limitation (see lines 463-467).

3.Page 7, lines 86-90, How to divide five climatic zones? Is it a common way? Any references for this division? Please add some description of weather conditions in five climatic zones.

Response: Thanks for pointing out this important issue. In the original version, we used the climatic divisions defined by China Meteorological Administration. In this revision, we renewed the zone-specific results according to the newly-issued definitions (with slight changes) and updated all descriptions, analyses and discussion relevant throughout this manuscript. We cited a reference and added some brief description about climatic characteristics in these zones. Please refer to lines 100-110.

4.Line 172 “univariable multivariate meta-regression models”, What does it mean? “Each model included a single meta-predictor”, do you mean that each potential effect modifier was analyzed separately? Why not perform multivariate meta regression? The climate, geography and socioeconomic conditions under consideration are correlated. In addition, the sources of these demographic and socioeconomic data should be mentioned.

Response: We apologize for this typo error, which should be "univariable meta-regression models".

We appreciate this useful suggestion to perform multivariable meta regression models in this heterogeneity test. In addition to the univariable meta-regression models, we fit multivariable meta regression models with all city characteristics included to explore their modifications in the overall temperature-mortality associations and the lag patterns for the cold effects and hot effects. Please refer to lines 206-207 in the statistical analysis section and lines 329-331 in the result section.

In this revision, we fit separate multivariable meta-regression models to evaluate the effect modifications by duration of central heating and other city-level characteristics in the mortality risk and burden due to non-optimum temperatures. Please refer to lines 209-211 in the statistical analysis section and lines 331-340 in the result section.

We also provided the sources of city-level demographic and socioeconomic data (see lines 131-135).

5.Both MMT and effect estimates varied by city. The authors clearly showed the impacts of climate and socioeconomic on the heterogeneity in effect estimates. MMT is an important indicator of the population's adaption to ambient temperature. It would be interesting to describe its geographic variations and give some explanation, too.

Response: This is a good suggestion to improve our manuscript. Following this comment, we plotted the associations of MMT with city characteristic to shed some light on how the local acclimatization varied by city (see lines 212-213 in the statistical analysis). We found MMT decreased with colder climate, larger temperature variation/range, higher latitude, and longer duration of central heating (see lines 341-343 in the results).

6.Figure 2. The overall lag structure of extreme cold effects. The trailing end of the curve goes upwards and shows significant effects even at lag 15 and afterwards. How do you explain this?

Response: Thanks for pointing out this issue. Most of previous studies have reported that the mortality effects of low temperature could last for 2 to 4 weeks. A simulation study in Japan showed the prolonged effects of cold temperature on cardiovascular mortality may be explained by the indirect effects of influenza (see lines 390-391). The cold effects need to be cautiously interpreted because of the possible residual confounding by the cold season and the influenza. Therefore, the lack of influenza data limited our ability to control it in our models. However, previous studies have revealed that the influenza accounted for a very small proportion of winter mortality and controlling for it would not substantially change the effect estimates of cold temperature. Please refer to lines 467-473 in the limitation section.

In this revision, we increased the degree of seasonality control from 8 df to 12 df per year (see lines 143-145). The updated lag structure (Figure 3) of cold effects showed the lag period was shortened and the upward trends at lags longer than 15 days almost disappeared (see lines 257-259). Accordingly, we updated all analyses, results and discussion using 12 df per year in smoothness of seasonality.

7.Page 9, lines 138, BLUP was mistyped as BULP.

Response: Revised.

8.Page 16, lines 278-282, according to Figure 4, the distribution from tropical monsoon zone seemed not to be similar with that from temperate continental zone.

Response: We apologize for this inadequate description. After re-fitting all the models by more aggressive control of seasonality and updated climatic divisions, we found the estimations on mortality RRs and burdens were statistically insignificant with much wider confidence intervals in the tropical monsoon zone and the temperate continental zone. Please refer to lines 312-314.

9.Page 43, the labels of x axis in two bottom figures should be lag(day).

Response: Revised as pointed out. Please refer to Figure S5.

Additional Questions:

Please enter your name: Chun-Quan Ou

Job Title: Prof.

Institution: Department of Biostatistics, School of Public Health

Reimbursement for attending a symposium?: No

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g. Footnotes and statements

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